Clinical trial results:
STRONG-HF: Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP TestinG, of Heart Failure Therapies

Summary

EudraCT number	2018-000486-37
Trial protocol	AT HR
Global end of trial date	13 October 2022

Results information

Result version number	v2 (current)
This version publication date	29 December 2022
First version publication date	28 July 2022
Version creation reason	• New data added to full data set This trial has been completed. Results need to be entered.
Summary attachment (see zip file)	Results unavailable (Unavailable results for Heart Initiative CHF201701 8Jul2022_signed.pdf)

Trial information

Trial identification

Sponsor protocol code	CHF201701

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03412201
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Heart Initiative
Sponsor organisation address	1426 NC Highway 54 Suite B, Durham, United States, 27713
Public contact	Beth Davison, Heart Initiative, +1 919-699-0888, bdavisonheartinitiative@gmail.org
Scientific contact	Beth Davison, Heart Initiative, +1 919-699-0888, bdavisonheartinitiative@gmail.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2022
Global end of trial reached?	Yes
Global end of trial date	13 October 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of optimization of medical therapy with beta-blocker; ACEi, ARB or ARNi; and MRAs on 180-day all-cause mortality or heart failure readmission in patients admitted with acute heart failure and clinical and biological signs of congestion.

Protection of trial subjects:

The study was in compliance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. Before enrolment, the study was approved by appropriate competent authorities and all sites obtained approval from the ethics committees. All patients provided written informed consent. A Data and Safety Monitoring Board assessed safety on an ongoing basis during the trial. All the local regulatory requirements pertinent to the safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Mozambique: 59
Country: Number of subjects enrolled	Nigeria: 165
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Tunisia: 12
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Bulgaria: 43
Country: Number of subjects enrolled	Slovakia: 33
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Russian Federation: 703
Country: Number of subjects enrolled	Argentina: 40
Country: Number of subjects enrolled	Colombia: 1
Worldwide total number of subjects	1078
EEA total number of subjects	92

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	547
From 65 to 84 years	521
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between May 10, 2018 and Sept 23, 2022 from 87 hospitals in 14 countries.

Pre-assignment

Screening details:

A total of 1641 patients were screened, of whom 556 did not pass screening (533 did not meet eligibility criteria, 7 decided not to participate, and 16 did not provide a reason). 1085 patients were randomly assigned to treatment, 7 of whom were randomly assigned in error, such that 1078 patients were validly assigned to either high intensity care o

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	High Intensity Care

Arm description:

Follow-up and management of heart failure medications provided by specialists at participating institutions. Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.

Arm type	Experimental
Investigational medicinal product name	beta-blocker, renin-angiotensin system blocker, mineralocorticoid receptor blocker
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.

Arm title	Usual Care

Arm description:

Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.

Arm type	Active comparator
Investigational medicinal product name	heart failure medications
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.

Number of subjects in period 1	High Intensity Care	Usual Care
Started	542	536
Completed	467	459
Not completed	75	77
Adverse event, serious fatal	40	48
Study terminated	25	23
Other reason	10	6

Baseline characteristics

Reporting groups	
Reporting group title	High Intensity Care
Reporting group description:	
Follow-up and management of heart failure medications provided by specialists at participating institutions. Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.	
Reporting group title	Usual Care
Reporting group description:	
Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.	

Reporting group values	High Intensity Care	Usual Care	Total
Number of subjects	542	536	1078
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	273	274	547
From 65-84 years	261	260	521
85 years and over	8	2	10
Age continuous Units: years			
arithmetic mean	62.9	63.0	
standard deviation	± 13.5	± 13.7	-
Gender categorical Units: Subjects			
Female	216	200	416
Male	326	336	662
Race Units: Subjects			
Black	115	115	230
White or Caucasian	418	414	832
Native American	1	0	1
Other	7	5	12
Pacific Islander	1	0	1
Missing	0	2	2
Left ventricular ejection fraction category Units: Subjects			
≤40%	365	366	731
>40%	177	170	347
Region of Enrollment Units: Subjects			

Africa	122	118	240
Europe	47	47	94
Russia	351	352	703
South America	22	19	41

End points

End points reporting groups

Reporting group title	High Intensity Care
Reporting group description:	
Follow-up and management of heart failure medications provided by specialists at participating institutions. Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.	
Reporting group title	Usual Care
Reporting group description:	
Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.	

Primary: 180-day All-cause Mortality or Heart Failure Readmission

End point title	180-day All-cause Mortality or Heart Failure Readmission
End point description:	
Cumulative risk of either readmission for heart failure or death at 180 days	
End point type	Primary
End point timeframe:	
180 days	

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506[1]	502[2]		
Units: Weighted Adjusted KM Event Rate (%)				
number (not applicable)	15.2	23.3		

Notes:

[1] - All patients randomized at sites that followed patients to day 180.

[2] - All patients randomized at sites that followed patients to day 180.

Statistical analyses

Statistical analysis title	Primary Outcome
Statistical analysis description:	
180-day All-cause Mortality or Heart Failure Readmission	
Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0021 [4]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	8.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.9
upper limit	13.2

Notes:

[3] - χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. Weighted average of difference in two cohorts. Main result down-weights result in early cohort proportional to half its sample size.

[4] - A chi-square test statistic with 1df computed as D^2/V, where D is the difference in event rates with associated variance V.

Secondary: Change in Quality of Life

End point title	Change in Quality of Life

End point description:

Change from baseline to 90 days in quality of life as measured using the EQ-5D visual analogue scale (VAS) which ranges from 0 to 100 with a higher score representing a better outcome. "EQ-5D" is the official name of a quality of life instrument developed by EuroQol.

End point type	Secondary

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461[5]	454[6]		
Units: score on a scale				
least squares mean (standard error)	10.72 (± 0.88)	7.22 (± 0.90)		

Notes:

[5] - Randomized patients with available data excluding subjects from Mozambique.

[6] - Randomized patients with available data excluding subjects from Mozambique.

Statistical analyses

Statistical analysis title	Change in Quality of Life

Statistical analysis description:

Change from baseline to 90 days in quality of life as measured using the EQ-5D visual analogue scale (VAS) which ranges from 0 to 100 with a higher score representing a better outcome. "EQ-5D" is the official name of a quality of life instrument developed by EuroQol. Subjects from Mozambique are excluded due to the unavailability of a linguistically validated translation of the EQ-5D in that country.

Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	915
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [7]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.49

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.74
upper limit	5.24

Notes:

[7] - Statistics are estimated from an ANCOVA model with fixed terms for treatment, LVEF (≤40% vs >40%), geographical region, and baseline value. Treatment effect is the adjusted mean difference between treatment groups.

Secondary: 180-day All-cause Mortality

End point title	180-day All-cause Mortality
End point description:	
Cumulative risk of death at 180 days	
End point type	Secondary
End point timeframe:	
180 days	

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506[8]	502[9]		
Units: Weighted Adjusted KM Event Rate (%)				
number (not applicable)	8.48	10.04		

Notes:

[8] - All patients randomized at sites that followed patients to day 180.

[9] - All patients randomized at sites that followed patients to day 180.

Statistical analyses

Statistical analysis title	180-day All-cause Mortality
Statistical analysis description:	
Cumulative risk of death at 180 days	
Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.42 [11]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	5.4

Notes:

[10] - χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. Weighted average of difference in two cohorts. Main result down-weights result in early

cohort proportional to half its sample size.

[11] - A chi-square test statistic with 1df computed as D^2/V, where D is the difference in event rates with associated variance V.

Secondary: 90-day All-cause Mortality or Heart Failure Readmission

End point title	90-day All-cause Mortality or Heart Failure Readmission

End point description:

Cumulative risk of either readmission for heart failure or death at 90 days

End point type	Secondary

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542[12]	536[13]		
Units: Adjusted KM Event Rate (%)				
number (not applicable)	10.4	13.8		

Notes:

[12] - All patients validly randomized.

[13] - All patients validly randomized.

Statistical analyses

Statistical analysis title	90-day All-cause Mortality or HF Readmission

Statistical analysis description:

Cumulative risk of either readmission for heart failure or death at 90 days

Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	1078
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.081 [15]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	7.3

Notes:

[14] - The difference in 90-day event rates is computed from Kaplan-Meier estimates adjusted for region and randomization stratification factor LVEF <=40/>40 using Mantel-Haenszel weights.

[15] - A chi-square test statistic with 1df computed as D^2/V, where D is the difference in event rates with associated variance V.

Other pre-specified: 180-day Cardiovascular Death

End point title	180-day Cardiovascular Death

End point description:

Cumulative risk of death due to cardiovascular cause at 180 days

End point type	Other pre-specified

End point timeframe:

180 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506[16]	502[17]		
Units: Weighted Adjusted KM Event Rate (%)				
number (not applicable)	6.9	9.3		

Notes:

[16] - All patients randomized at sites that followed patients to day 180.

[17] - All patients randomized at sites that followed patients to day 180.

Statistical analyses

Statistical analysis title	180-day Cardiovascular Death
Statistical analysis description:	
Cumulative risk of death due to cardiovascular cause at 180 days	
Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.19 [19]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	6.1

Notes:

[18] - χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. Weighted average of difference in two cohorts. Main result down-weights result in early cohort proportional to half its sample size.

[19] - A chi-square test statistic with 1df computed as D^2/V, where D is the difference in event rates with associated variance V.

Other pre-specified: 90-day Cardiovascular Death

End point title	90-day Cardiovascular Death
End point description:	
Cumulative risk of death due to cardiovascular cause at 90 days	
End point type	Other pre-specified
End point timeframe:	
90 days	

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542[20]	536[21]		
Units: Adjusted KM Event Rate (%)				
number (not applicable)	3.3	5.4		

Notes:

[20] - All patients validly randomized.

[21] - All patients validly randomized.

Statistical analyses

Statistical analysis title	90-day Cardiovascular Death

Statistical analysis description:

Cumulative risk of death due to cardiovascular cause at 90 days

Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	1078
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.086 [23]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	4.6

Notes:

[22] - The difference in 90-day event rates is computed from Kaplan-Meier estimates adjusted for region and randomization stratification factor LVEF <=40/>40 using Mantel-Haenszel weights.

[23] - A chi-square test statistic with 1df computed as D^2/V, where D is the difference in event rates with associated variance V.

Other pre-specified: 90-day All-cause Mortality

End point title	90-day All-cause Mortality

End point description:

Cumulative risk of death at 90 days

End point type	Other pre-specified

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542[24]	536[25]		
Units: Adjusted KM Event Rate (%)				
number (not applicable)	4.3	5.7		

Notes:

[24] - All patients validly randomized.

[25] - All patients validly randomized.

Statistical analyses

Statistical analysis title	90-day All-cause Mortality
Statistical analysis description:	
Cumulative risk of death at 90 days	
Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	1078
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.28 [27]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	4

Notes:

[26] - The difference in 90-day event rates is computed from Kaplan-Meier estimates adjusted for region and randomization stratification factor LVEF <=40/>40 using Mantel-Haenszel weights.

[27] - A chi-square test statistic with 1df computed as D^2/V, where D is the difference in event rates with associated variance V.

Other pre-specified: 180-day Heart Failure Readmission	
End point title	180-day Heart Failure Readmission
End point description:	
Cumulative risk of readmission for heart failure at 180 days	
End point type	Other pre-specified
End point timeframe:	
180 days	

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	506[28]	502[29]		
Units: Weighted Adjusted KM Event Rate (%)				
number (not applicable)	9.5	17.1		

Notes:

[28] - All patients randomized at sites that followed patients to day 180.

[29] - All patients randomized at sites that followed patients to day 180.

Statistical analyses

Statistical analysis title	180-day Heart Failure Readmission
Statistical analysis description:	
Cumulative risk of readmission for heart failure at 180 days	
Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	1008
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.0011 [31]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3
upper limit	12.1

Notes:

[30] - χ^2 test of the difference in 180-day event rates between groups, calculated from the difference in Kaplan-Meier estimates of the cumulative risks at 180 days adjusted for LVEF (≤40% vs >40%) and geographical region using Mantel-Haenszel weights, and from the variance calculated from their associated SEs. Weighted average of difference in two cohorts. Main result down-weights result in early cohort proportional to half its sample size.

[31] - A chi-square test statistic with 1df computed as D^2/V, where D is the difference in event rates with associated variance V.

Other pre-specified: 90-day Heart Failure Readmission

End point title	90-day Heart Failure Readmission
End point description:	
Cumulative risk of readmission for heart failure at 90 days	
End point type	Other pre-specified
End point timeframe:	
90 days	

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542[32]	536[33]		
Units: Adjusted KM Event Rate (%)				
number (not applicable)	6.9	9.5		

Notes:

[32] - All patients validly randomized.

[33] - All patients validly randomized.

Statistical analyses

Statistical analysis title	90-day Heart Failure Readmission
Statistical analysis description:	
Cumulative risk of readmission for heart failure at 90 days	
Comparison groups	High Intensity Care v Usual Care

Number of subjects included in analysis	1078
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.13 [35]
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	5.8

Notes:

[34] - The difference in 90-day event rates is computed from Kaplan-Meier estimates adjusted for region and randomization stratification factor LVEF <=40/>40 using Mantel-Haenszel weights.
[35] - A chi-square test statistic with 1df computed as D^2/V, where D is the difference in event rates with associated variance V.

Other pre-specified: Finkelstein-Schoenfeld Hierarchical Composite

End point title	Finkelstein-Schoenfeld Hierarchical Composite

End point description:

Hierarchical composite endpoint comprising death, heart failure readmissions, and EQ-VAS analyzed using Finkelstein-Schoenfeld methodology

End point type	Other pre-specified

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542[36]	536[37]		
Units: percentage of favorable comparisons				
number (not applicable)	40.4	29.4		

Notes:

[36] - All patients validly randomized.

[37] - All patients validly randomized.

Statistical analyses

Statistical analysis title	Finkelstein-Schoenfeld Hierarchical Composite

Statistical analysis description:

Hierarchical composite endpoint comprising death, heart failure readmissions, and EQ-VAS analyzed using Finkelstein-Schoenfeld methodology.

Comparison groups	High Intensity Care v Usual Care

Number of subjects included in analysis	1078
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.0002 [39]
Method	van Elteren's test
Parameter estimate	Mann-Whitney odds
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	1.46

Notes:

[38] - Treatment effect is the Mann-Whitney odds adjusted for LVEF (≤40% vs >40%) and geographical region, using Mantel-Haenzsel weights.
[39] - P-value calculated from van Elteren's test stratified by LVEF (≤40% vs >40%) and geographical region, using modified ridit scores.

Other pre-specified: Change in NT-proBNP

End point title	Change in NT-proBNP
End point description:	
Change from baseline to 90 days in NT-proBNP on the log scale	
End point type	Other pre-specified
End point timeframe:	
90 days	

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476[40]	475[41]		
Units: ratio				
least squares mean (standard error)	0.436 (± 1.072)	0.564 (± 1.074)		

Notes:

[40] - Randomized patients with available data.

[41] - Randomized patients with available data.

Statistical analyses

Statistical analysis title	Change in NT-proBNP
Statistical analysis description:	
Change from baseline to 90 days in NT-proBNP on the log scale	
Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	951
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.0003 [43]
Method	ANCOVA
Parameter estimate	Adjusted Geometric Mean Ratio
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.89

Notes:

[42] - Comparison of the ratio of post-baseline value over the baseline value adjusted for the specified covariates between the high-intensity care group and the usual care group.
[43] - Statistics are estimated based on an Analysis of Covariance (ANCOVA) model with fixed terms for treatment, LVEF <=40/>40, region, and baseline log-transformed NT-proBNP value.

Other pre-specified: Change in Weight

End point title	Change in Weight

End point description:

Change from baseline to 90 days in weight in kg

End point type	Other pre-specified

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	489[44]	479[45]		
Units: kg				
least squares mean (standard error)	-1.78 (± 0.282)	-0.42 (± 0.290)		

Notes:

[44] - Randomized patients with available data.

[45] - Randomized patients with available data.

Statistical analyses

Statistical analysis title	Change in Weight

Statistical analysis description:

Change from baseline to 90 days in weight in kg

Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	968
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [46]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.91
upper limit	-0.8

Notes:

[46] - Statistics are estimated from an ANCOVA model with fixed terms for treatment, LVEF (≤40% vs >40%), geographical region, and baseline value. Treatment effect is the adjusted mean difference between treatment groups.

Other pre-specified: Changes in Signs and Symptoms of Congestion: NYHA Class

End point title	Changes in Signs and Symptoms of Congestion: NYHA Class

End point description:

Changes from baseline to 90 days in New York Heart Association (NYHA) class which ranges from I to IV with a higher class representing a worse outcome.

End point type	Other pre-specified

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	495[47]	488[48]		
Units: participants				
NYHA at baseline: I	34	27		
NYHA at baseline: II	288	306		
NYHA at baseline: III	170	152		
NYHA at baseline: IV	3	3		
NYHA at day 90: I	116	76		
NYHA at day 90: II	297	288		
NYHA at day 90: III	77	107		
NYHA at day 90: IV	5	17		

Notes:

[47] - Randomized patients with available data.

[48] - Randomized patients with available data.

Statistical analyses

Statistical analysis title	Changes in Signs and Symptoms of Congestion: NYHA

Statistical analysis description:

Changes from baseline to 90 days in New York Heart Association (NYHA) class which ranges from I to IV with a higher class representing a worse outcome.

Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	983
Analysis specification	Pre-specified
Analysis type	superiority[49]
P-value	< 0.0001 [50]
Method	van Elteren’s test
Parameter estimate	Mann-Whitney odds
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.22
upper limit	1.53

Notes:

[49] - Treatment effect presented as Mann-Whitney odds stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.
A Mann-Whitney odds value of >1·0 favours high-intensity care.

[50] - P value from van Elteren's test stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.

Other pre-specified: Changes in Signs and Symptoms of Congestion: Orthopnea

End point title	Changes in Signs and Symptoms of Congestion: Orthopnea

End point description:

Changes from baseline to 90 days in orthopnea rated on a scale from 0 to 3 with a higher score representing a worse outcome.

End point type	Other pre-specified

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	493[51]	486[52]		
Units: participants				
0: None at baseline	308	304		
1: 1 pillow (10 cm) at baseline	168	165		
2: 2 pillows (20 cm) at baseline	16	16		
3: >30 degrees at baseline	1	1		
0: None at day 90	381	339		
1: 1 pillow (10 cm) at day 90	99	124		
2: 2 pillows (20 cm) at day 90	10	19		
3: >30 degrees at day 90	3	4		

Notes:

[51] - Randomized patients with available data.

[52] - Randomized patients with available data.

Statistical analyses

Statistical analysis title	Changes in Orthopnea

Statistical analysis description:

Changes from baseline to 90 days in orthopnea rated on a scale from 0 to 3 with a higher score representing a worse outcome.

Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	979
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.0048 [54]
Method	van Elteren’s test
Parameter estimate	Mann-Whitney odds
Point estimate	1.17

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	1.29

Notes:

[53] - Treatment effect presented as Mann-Whitney odds stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.
A Mann-Whitney odds value of >1·0 favours high-intensity care.
[54] - P value from van Elteren's test stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.

Other pre-specified: Changes in Signs and Symptoms of Congestion: Peripheral Edema

End point title	Changes in Signs and Symptoms of Congestion: Peripheral Edema

End point description:

Changes from baseline to 90 days in peripheral edema rated on a scale from 0 to 3 with a higher score representing a worse.

End point type	Other pre-specified

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	491[55]	483[56]		
Units: participants				
None at baseline	286	278		
1+ at baseline	175	173		
2+ at baseline	29	27		
3+ at baseline	1	5		
None at day 90	384	315		
1+ at day 90	91	130		
2+ at day 90	15	33		
3+ at day 90	1	5		

Notes:

[55] - Randomized patients with available data.

[56] - Randomized patients with available data.

Statistical analyses

Statistical analysis title	Changes in Peripheral Edema

Statistical analysis description:

Changes from baseline to 90 days in peripheral edema rated on a scale from 0 to 3 with a higher score representing a worse outcome.

Comparison groups	High Intensity Care v Usual Care

Number of subjects included in analysis	974
Analysis specification	Pre-specified
Analysis type	superiority[57]
P-value	= 0.0002 [58]
Method	van Elteren's test
Parameter estimate	Mann-Whitney odds
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	1.44

Notes:

[57] - Treatment effect presented as Mann-Whitney odds stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.
A Mann-Whitney odds value of >1·0 favours high-intensity care.

[58] - P value from van Elteren's test stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.

Other pre-specified: Changes in Signs and Symptoms of Congestion: Rales

End point title	Changes in Signs and Symptoms of Congestion: Rales

End point description:

Changes from baseline to 90 days in rales rated on a scale from 0 to 3 with a higher score representing a worse outcome.

End point type	Other pre-specified

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	490[59]	479[60]		
Units: participants				
0: None at baseline	417	411		
1: <1/3 at baseline	63	63		
2: 1/3 to 2/3 at baseline	10	5		
3: >2/3 at baseline	0	0		
0: None at day 90	454	421		
1: <1/3 at day 90	33	57		
2: 1/3 to 2/3 at day 90	3	1		
3: >2/3 at day 90	0	0		

Notes:

[59] - Randomized patients with available data.

[60] - Randomized patients with available data.

Statistical analyses

Statistical analysis title	Changes in Rales

Statistical analysis description:

Changes from baseline to 90 days in rales rated on a scale from 0 to 3 with a higher score representing a worse outcome.

Comparison groups	High Intensity Care v Usual Care
Number of subjects included in analysis	969
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	= 0.073 [62]
Method	van Elteren's test
Parameter estimate	Mann-Whitney odds
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.15

Notes:

[61] - Treatment effect presented as Mann-Whitney odds stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.
A Mann-Whitney odds value of >1·0 favours high-intensity care.

[62] - P value from van Elteren's test stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.

Other pre-specified: Changes in Signs and Symptoms of Congestion: JVP

End point title	Changes in Signs and Symptoms of Congestion: JVP

End point description:

Changes from baseline to 90 days in jugular venous pulse (JVP) rated on a scale from 1 to 3 with a higher score representing a worse outcome.

End point type	Other pre-specified

End point timeframe:

90 days

End point values	High Intensity Care	Usual Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	450[63]	428[64]		
Units: participants				
1: <6 cm at baseline	383	359		
2: 6–10 cm at baseline	64	66		
3: >10 cm at baseline	3	3		
1: <6 cm at day 90	418	377		
2: 6–10 cm at day 90	30	40		
3: >10 cm at day 90	2	11		

Notes:

[63] - Randomized patients with available data.

[64] - Randomized patients with available data.

Statistical analyses

Statistical analysis title	Changes in JVP

Statistical analysis description:

Changes from baseline to 90 days in jugular venous pulse (JVP) rated on a scale from 1 to 3 with a higher score representing a worse outcome.

Comparison groups	High Intensity Care v Usual Care

Number of subjects included in analysis	878
Analysis specification	Pre-specified
Analysis type	superiority[65]
P-value	= 0.015 [66]
Method	van Elteren’s test
Parameter estimate	Mann-Whitney odds
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.21

Notes:

[65] - Treatment effect presented as Mann-Whitney odds stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.
A Mann-Whitney odds value of >1·0 favours high-intensity care.

[66] - P value from van Elteren's test stratified by LVEF (≤40% vs >40%), geographical region, and baseline value.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 90	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	High Intensity Care
Reporting group description:	
Follow-up and management of heart failure medications provided by specialists at participating institutions. Doses of oral heart failure medications optimized within 2 weeks, provided clinical assessments and laboratory measures indicate that it is safe to increase doses.	
Reporting group title	Usual Care
Reporting group description:	
Follow-up and management of heart failure medications provided by the patient's general physician and/or cardiologist according to local medical standards.	

Serious adverse events	High Intensity Care	Usual Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 542 (16.24%)	92 / 536 (17.16%)	
number of deaths (all causes)	23	30	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			

Chemotherapy			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
High frequency ablation			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	5 / 542 (0.92%)	10 / 536 (1.87%)	
occurrences causally related to treatment / all	0 / 5	0 / 10	
deaths causally related to treatment / all	0 / 5	0 / 10	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	1 / 542 (0.18%)	3 / 536 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pulmonary oedema			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	2 / 542 (0.37%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 542 (0.55%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 542 (0.37%)	2 / 536 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial flutter			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	38 / 542 (7.01%)	47 / 536 (8.77%)	
occurrences causally related to treatment / all	0 / 42	0 / 52	
deaths causally related to treatment / all	0 / 7	0 / 10	
Cardiac failure acute			
subjects affected / exposed	0 / 542 (0.00%)	2 / 536 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 542 (0.18%)	6 / 536 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	1 / 542 (0.18%)	2 / 536 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	4 / 542 (0.74%)	2 / 536 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 1	
Hemianopia homonymous			

subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 542 (0.00%)	2 / 536 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia strangulated			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatitis acute			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	3 / 542 (0.55%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteochondrosis			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	10 / 542 (1.85%)	6 / 536 (1.12%)	
occurrences causally related to treatment / all	0 / 10	0 / 6	
deaths causally related to treatment / all	0 / 4	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	4 / 542 (0.74%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia viral			
subjects affected / exposed	7 / 542 (1.29%)	3 / 536 (0.56%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	High Intensity Care	Usual Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	157 / 542 (28.97%)	77 / 536 (14.37%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign gastric neoplasm			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 542 (0.55%)	2 / 536 (0.37%)	
occurrences (all)	3	2	
Hypertensive crisis			
subjects affected / exposed	4 / 542 (0.74%)	2 / 536 (0.37%)	
occurrences (all)	4	2	
Hypotension			
subjects affected / exposed	26 / 542 (4.80%)	2 / 536 (0.37%)	
occurrences (all)	33	2	
Orthostatic hypotension			
subjects affected / exposed	3 / 542 (0.55%)	0 / 536 (0.00%)	
occurrences (all)	3	0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Chemotherapy			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 542 (0.37%)	1 / 536 (0.19%)	
occurrences (all)	2	1	
Chest pain			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Fatigue			

subjects affected / exposed	2 / 542 (0.37%)	2 / 536 (0.37%)	
occurrences (all)	2	2	
Pain			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Swelling			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Immune system disorders			
Amyloidosis			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Gynaecomastia			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Metrorrhagia			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 542 (0.37%)	1 / 536 (0.19%)	
occurrences (all)	2	1	
Dyspnoea			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences (all)	1	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Angiocardiogram			

subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	3 / 542 (0.55%)	0 / 536 (0.00%)	
occurrences (all)	3	0	
Blood potassium increased			
subjects affected / exposed	2 / 542 (0.37%)	0 / 536 (0.00%)	
occurrences (all)	2	0	
Blood pressure decreased			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	7 / 542 (1.29%)	6 / 536 (1.12%)	
occurrences (all)	8	7	
Blood uric acid increased			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Glomerular filtration rate decreased			
subjects affected / exposed	2 / 542 (0.37%)	0 / 536 (0.00%)	
occurrences (all)	2	0	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	3 / 542 (0.55%)	0 / 536 (0.00%)	
occurrences (all)	4	0	
Platelet count decreased			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Contusion			

subjects affected / exposed	2 / 542 (0.37%)	3 / 536 (0.56%)	
occurrences (all)	2	3	
Humerus fracture			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Skin laceration			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Toxicity to various agents			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Arrhythmia			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	2 / 542 (0.37%)	1 / 536 (0.19%)	
occurrences (all)	2	1	
Bradycardia			
subjects affected / exposed	4 / 542 (0.74%)	2 / 536 (0.37%)	
occurrences (all)	4	2	
Cardiac failure			
subjects affected / exposed	45 / 542 (8.30%)	30 / 536 (5.60%)	
occurrences (all)	51	31	
Cardiac failure acute			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Cardiac failure chronic			
subjects affected / exposed	3 / 542 (0.55%)	1 / 536 (0.19%)	
occurrences (all)	3	1	

Coronary artery disease			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 542 (0.00%)	5 / 536 (0.93%)	
occurrences (all)	0	5	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	4 / 542 (0.74%)	0 / 536 (0.00%)	
occurrences (all)	4	0	
Dizziness exertional			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	2 / 542 (0.37%)	1 / 536 (0.19%)	
occurrences (all)	2	1	
Loss of consciousness			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	2 / 542 (0.37%)	0 / 536 (0.00%)	
occurrences (all)	2	0	
Somnolence			

subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 542 (0.55%)	0 / 536 (0.00%)	
occurrences (all)	3	0	
Anaemia of chronic disease			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences (all)	1	1	
Leukocytosis			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	2 / 542 (0.37%)	2 / 536 (0.37%)	
occurrences (all)	2	2	
Diarrhoea			
subjects affected / exposed	3 / 542 (0.55%)	1 / 536 (0.19%)	
occurrences (all)	3	1	
Dry mouth			
subjects affected / exposed	2 / 542 (0.37%)	0 / 536 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	3 / 542 (0.55%)	0 / 536 (0.00%)	
occurrences (all)	3	0	
Eructation			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			

subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 542 (0.37%)	0 / 536 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences (all)	1	1	
Skin ulcer			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Stasis dermatitis			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 542 (0.37%)	0 / 536 (0.00%)	
occurrences (all)	2	0	
Renal failure			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Renal impairment			
subjects affected / exposed	12 / 542 (2.21%)	0 / 536 (0.00%)	
occurrences (all)	14	0	
Urinary retention			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	2 / 542 (0.37%)	1 / 536 (0.19%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Gouty arthritis			
subjects affected / exposed	2 / 542 (0.37%)	1 / 536 (0.19%)	
occurrences (all)	2	1	
Hypercreatinaemia			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	4 / 542 (0.74%)	0 / 536 (0.00%)	
occurrences (all)	4	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Corona virus infection			
subjects affected / exposed	4 / 542 (0.74%)	2 / 536 (0.37%)	
occurrences (all)	4	2	
Influenza			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Malaria			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	8 / 542 (1.48%)	3 / 536 (0.56%)	
occurrences (all)	8	3	
Peritonitis			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Pharyngitis			

subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Pulpitis dental			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	3 / 542 (0.55%)	5 / 536 (0.93%)	
occurrences (all)	3	5	
Sepsis			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Dehydration			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Fluid retention			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Gout			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	

Hyperglycaemia			
subjects affected / exposed	0 / 542 (0.00%)	1 / 536 (0.19%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	17 / 542 (3.14%)	0 / 536 (0.00%)	
occurrences (all)	18	0	
Hyperuricaemia			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 542 (0.18%)	1 / 536 (0.19%)	
occurrences (all)	1	1	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 542 (0.18%)	0 / 536 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 June 2019	After the study started, the protocol was amended to add a patient contact at 180 days for safety.
11 January 2021	After the study started, the protocol was amended to increase study power by changing the timing of assessment for the primary endpoint from 90 to 180 days and increasing target enrolment from 900 to 1800.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated on Sept 23, 2022, following the recommendation of the DSMB due to a larger-than-expected difference in risk of the primary endpoint between the groups based on an analysis when 1069 total patients had been randomly assigned.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34529313

http://www.ncbi.nlm.nih.gov/pubmed/31423712

http://www.ncbi.nlm.nih.gov/pubmed/36356631